Vaccines and Related Biological Products Advisory Committee

FDA Briefing Document

Use of Serum Bactericidal Antibody as an Immunological Correlate for Demonstrating Effectiveness of Meningococcal Conjugate Vaccines (Serogroups A, C, Y, W-135) Administered to Children Less Than 2 Years of Age

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Executive Summary

Neisseria meningitidis is a primary cause of bacterial meningitis, especially in young children. Meningococcal meningitis can occur with or without meningococcemia. A timely clinical diagnosis is difficult, and, even with available treatments, approximately 10-20% of individuals with invasive meningococcal disease experience sequelae (e.g., limb loss, neurosensory hearing loss, cognitive deficits, seizure disorder). The highest incidence of meningococcal disease occurs in children younger than one year of age.

In the U.S., three meningococcal vaccines are licensed and available for the prevention of invasive disease due to *N meningitidis* serogroups A, C, W-135 and Y: a tetravalent meningococcal polysaccharide vaccine, MPSV4 (Menomune A/C/Y/W-135, Sanofi Pasteur, Inc., Swiftwater, PA, USA), and two tetravalent meningococcal conjugate vaccines, MenACWY-D (Menactra, Sanofi Pasteur, Inc., Swiftwater, PA, USA), and MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics S.r.l., Bellaria-Rosia, Italy). Licensure of MPSV4 was supported by (a) Clinical effectiveness of meningococcal serogroup A and serogroup C polysaccharide vaccines. (b) Data supporting the use of serum bactericidal antibody as an immunological correlate. (c) Bactericidal antibody responses to each of the antigens in MSPV4 after vaccination. Licensure approaches for approval of new meningococcal conjugate vaccines using an immunological correlate was discussed at a Vaccines and Related Biological Products Advisory Committee Meeting, held on September 15, 1999. The committee concluded that vaccine effectiveness could be estimated by serum bactericidal antibodies and advised that comparative studies between U.S. licensed and investigational meningococcal vaccines using bactericidal antibody measurements could be the basis for inferring effectiveness of newer vaccines. Thus, effectiveness of MenACWY-D and MenACWY-CRM vaccines were inferred from demonstration of immunological non-inferiority to a U.S. licensed meningococcal vaccine. Because the MSPV4 was approved for use in children 2 years of age and older, the lower age limit for use of MenACWY-D and MenACWY-CRM using this approach was also limited to 2 years of age.

Multivalent meningococcal conjugate vaccines intended for infant and/or toddler use are in development or currently indicated for older children. Clinical efficacy studies to support U.S. licensure would be the clearest demonstration of benefit of meningococcal conjugate vaccines to prevent serogroup A, C, W-135 and Y disease in children < 2 years old, however, such studies would be difficult to conduct due to low incidence and sporadic occurrence of cases of disease in the U.S. Since a meningococcal conjugate vaccine has not been licensed in the U.S. in children younger than 2 years old, effectiveness of a new meningococcal conjugate vaccine in young children would be predicted by measurement of a serum bactericidal antibody titer considered to be protective, rather than a comparison of antibody responses to a meningococcal vaccine with established effectiveness. Use of serum bactericidal antibody measurements to predict protection from meningococcal diseases in children <2 years old is supported by (a) The central role of anti-meningococcal bactericidal antibodies, measured by serum bactericidal activity, in immunity to meningococcal disease in all age groups. (b) Clinical experience with meningococcal polysaccharide and conjugate vaccines in older children and adults (c) Clinical experience in young children with vaccines using similar conjugation technology, such as Hib, pneumococcal and meningococcal C conjugate vaccines. (d) A serum bactericidal assay method that can reliably measure functional activity *in vitro*. For purposes of U.S. licensure, meningococcal conjugate vaccine-induced bactericidal antibody responses, measured by a serum bactericidal assay, appears to be predictive of vaccine effectiveness against meningococcal disease.

Epidemiology of meningococcal disease in young children

In the U.S., the majority of invasive meningococcal disease is due to serogroups B, Y and C. More than 98% of cases are sporadic, and localized serogroup C outbreaks have been more frequent since 1991. Also, the overall proportion of meningococcal disease due to serogroup Y increased from 2%, during 1989-1991, to 30% during 1992-1996, and to 37% in 1997-2002. In the last three decades, cyclical peaks in meningococcal disease incidence were observed at approximately 10 year intervals. In the 1990's, the overall incidence of meningococcal disease in the U.S. population peaked at 1.7/ 100,000 population, and decreased to 0.35/ 100,000 population in 2007.[1] Declines in disease burden were observed for all serogroups and among all age groups. The case-fatality rate for meningococcal disease was about 15%.

The highest rate of meningococcal disease in the U.S. occurs in children younger than one year of age. In 1999-2008, serogroup B accounted on average for > 50% of cases of meningococcal disease that occurred annually in children <1 year old. Serogroup Y on average caused ~30% of annual meningococcal cases during the same time period. In 2009, preliminary data indicated that the incidence of meningococcal disease in children <1 year old due to serogroups C, W-135/non-groupable, Y and B was 0.19, 0.19, 0.58 and 1.54/ 100,000 population, respectively. The largest disease burden occurred among children ages 0 to 8 months.[2]

***N meningitidis* capsular polysaccharides**

Classification of *N meningitidis* into serogroups is based on the biochemical composition of the polysaccharide capsule. Five serogroups (A, B, C, W135 and Y) cause the majority of clinical disease.

Meningococcal capsular polysaccharides are among a number of bacterial antigens that contribute to immune evasion and pathogenesis. Capsular polysaccharides inhibit phagocytosis by polymorphonuclear leukocytes, and are themselves conserved cell surface antigens. In the context of polysaccharide meningococcal vaccine development, serogroup B capsular polysaccharides are poorly immunogenic. Serogroup A and C polysaccharide vaccine(s) immunogenicity was largely a function of the molecular size of the polysaccharide.

Pathogenesis of infection

Meningococcal isolates from blood or CSF are typically encapsulated strains. Unencapsulated strains, frequently isolated from the nasopharynx of asymptomatic carriers, are generally of low virulence. Meningococci that overcome host mucosal defenses enter the bloodstream and seed the cerebral spinal fluid (CSF). If bacterial multiplication is rapid, meningococcemia and shock ensue. Intravascular protection against meningococcal infection is mediated by antibody and complement recognition of the bacterial surface, which activate complement pathways leading to phagocytosis or to direct bacterial cell lysis. The polysaccharide capsule contributes to immune evasion and pathogenesis. In this regard, complement activation by the classical pathway occurs via polysaccharide-specific antibody binding to the meningococcal cell surface. The alternative pathway is activated by C3b complement component binding to the bacterial surface, and occurs to a lesser extent in immune individuals than in non-immune individuals. Both pathways of complement activation lead to formation of a lytic membrane attack complex (MAC), which directly results in cell killing. Complement deposition on the cell surface also inhibits phagocytosis.

Bactericidal antibodies and immunity to meningococcal disease

Immunity to systemic meningococcal disease, in both children and adults, can occur via anti-capsular antibody mediated complement pathway activation that leads to formation of a lytic membrane attack complex (MAC), which directly results in cell killing (bactericidal activity).

Serum bactericidal antibodies in newborn infants reflect passively acquired maternal antibodies. During the first few months of life, when maternal antibodies persist, meningococcal disease is uncommon. As maternal antibodies decline, susceptibility of infants to meningococcal disease increases. The presence of anti-meningococcal antibodies in maternal sera, as measured by serum bactericidal activity against pathogenic *N meningitidis* strains (serogroups A, B, C, W-135), was shown to correspond with serum bactericidal activity in infant-matched sera. [3]

An association between anti-meningococcal antibodies, measured by bactericidal activity in serum, and immunity to meningococcal disease is observed in all age groups.[4] Studies by Goldschneider et al. showed an inverse relation between the incidence of meningococcal disease and bactericidal activity against pathogenic *N meningitidis* strains (serogroups A, B, and C), in sera obtained from 282 children and 567 young adults. Sera were tested using an assay with a human complement source. Less than 20% of individuals 6-12 months old had sera with bactericidal activity against pathogenic *N meningitidis* strains, which corresponded to age when the incidence of meningococcal disease was highest. Bactericidal activity was noted in 50%-80% of sera from older children and in 65%-85% of adults, which corresponded to gradual declines in disease incidence.[4]

The role of serum antibodies in immunity to disease was also recognized in a study among military recruits.[4] At the start of basic training, approximately 80% of recruits had meningococcal group C bactericidal antibodies present in their sera. An assay with a human complement source was used for serum testing. Individuals who had meningococcal-specific bactericidal activity measured in the serum frequently became asymptomatic carriers and did not develop systemic meningococcal disease. In contrast, almost all individuals who did develop systemic disease were recruits with sera that lacked bactericidal activity to pathogenic meningococcal strains. Meningococcal disease occurred in approximately 40% of individuals who originally lacked serum bactericidal activity to the same strain and acquired the strain in the nasopharynx.

Persons with inherited serum complement component C5, C6, C7, or C8 deficiency (late complement component deficiencies; LCCD) are markedly susceptible to systemic meningococcal disease. C5, C6, C7 and C8 in part are needed to assemble the membrane attack complex needed for complement-mediated bactericidal activity. In individuals with LCCD, the risk of developing meningococcal disease is approximately 5000-7000 times higher compared to complement-sufficient individuals. Approximately 40-50% of LCCD individuals experience recurrent meningococcal infections.[5]

Regulatory History of Meningococcal Vaccines Licensed in the U.S.

In the U.S., three meningococcal vaccines that contain purified capsular polysaccharide(s) alone or conjugated to a carrier protein are licensed and available for the prevention of invasive disease due to *N meningitidis* serogroups A, C, W-135 and Y: a tetravalent meningococcal polysaccharide vaccine, MPSV4 (Menomune A/C/Y/W-135, Sanofi Pasteur, Inc., Swiftwater, PA, USA), and two tetravalent meningococcal conjugate vaccines, MenACWY-D (Menactra, Sanofi Pasteur, Inc., Swiftwater, PA, USA), and MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics S.r.l., Bellaria-Rosia, Italy).

MPSV4 is licensed for use in individuals 2 years and older. Effectiveness was demonstrated based on serum bactericidal antibody as an immune correlate of protection. The importance of bactericidal antibody was supported by immunogenicity data described in the preceding section *[Bactericidal antibodies and immunity to meningococcal disease]*. MPSV4 effectiveness was supported by clinical efficacy data from studies with similar meningococcal monovalent A and C

and bivalent A/C polysaccharide vaccines. Serum bactericidal antibody responses following MPSV4 could be bridged to responses of vaccines with established effectiveness, but were the primary basis for demonstrating effectiveness of serogroup W135 and Y components. Due to the low incidence of serogroup W-135 and Y disease, vaccine effectiveness of these two components was not directly measured in a clinical efficacy trial.

Licensure approaches for approval of new meningococcal conjugate vaccines using an immunological correlate was discussed at a Vaccines and Related Biological Products Advisory Committee Meeting, held on September 15, 1999.[6] The committee concluded that vaccine effectiveness could be estimated by bactericidal antibodies measured in serum and advised that studies comparing US-licensed and investigational meningococcal vaccines using bactericidal antibody measurements could be the basis for inferring effectiveness of newer vaccines. Thus, effectiveness of MenACWY-D and MenACWY-CRM vaccines was inferred from demonstrated immunological non-inferiority to a U.S. licensed meningococcal vaccine. Because the polysaccharide vaccine was approved for use in children 2 years of age and older, the lower age limit for use of MenACWY-D and MenACWY-CRM using this approach was also limited to 2 years of age.

Evaluation of meningococcal conjugate vaccines in children younger than two years of age
Multivalent meningococcal conjugate vaccines intended for infant and/or toddler use are in development[7;8], and license application(s) and supplements are currently under review at FDA. Clinical efficacy studies to support U.S. licensure would be the clearest demonstration of benefit of meningococcal conjugate vaccines to prevent serogroups A, C, W-135 and Y disease in children <2 years old; however, such studies would be difficult to conduct in the U.S. due to low meningococcal disease incidence and cases of disease are sporadic. When clinical efficacy trials are not feasible, effectiveness of a vaccine inferred from an immunological correlate could be an alternative licensure approach. Since a meningococcal conjugate vaccine has not been licensed in the U.S. for children <2 years old, vaccine effectiveness that corresponds to pre-specified serum bactericidal antibody titer considered to be protective, rather than a comparison of antibody responses to a vaccine with established effectiveness. In this regard, demonstration of immunogenicity of meningococcal conjugate vaccines in children <2 years old using SBA is supported by:

1. Studies by Goldschneider et al. showing that anti-meningococcal bactericidal antibodies, measured by serum bactericidal activity, were a predictor of immunity to meningococcal disease in all age groups.
2. Evidence of efficacy in field trials of meningococcal polysaccharide vaccines and immunogenicity of multivalent meningococcal conjugate vaccines in older children and adults.
3. Experience with use of Hib, pneumococcal and meningococcal C conjugate vaccines in infants and toddlers.
4. An assay method that can reliably measure functional activity *in vitro*. Antibody-mediated complement-dependent bactericidal killing is a mechanism by which antibodies *in vivo* confer immunity to meningococcal disease. For immunogenicity evaluations of meningococcal conjugate vaccines in infants/toddlers, a direct comparison of antibody responses to a U.S. licensed vaccine is not possible since a U.S licensed meningococcal vaccine is not available for this age group. Therefore, the serologic assays used in clinical trials need to accurately assess antibody responses at a titer indicative of protection rather than as assessment of immune responses between two vaccines. Functional antibody responses following

meningococcal conjugate vaccination, measured by a serum bactericidal assay, would be a reliable immune measure of vaccine effectiveness.

1. *The role of anti-meningococcal antibody in immunity to systemic meningococcal disease*

Studies by Goldschneider et al.[3] established the importance of functional antibodies, measured by serum bactericidal activity, as a predictor of meningococcal disease protection in all age groups. Details of the studies were described the section entitled *Bactericidal antibodies and immunity to meningococcal disease*. Markedly increased susceptibility to meningococcal infections in individuals with late complement component deficiencies supports complement-mediated bacteriolysis as a major mechanism of disease protection.

2. Clinical effectiveness and immunogenicity of meningococcal polysaccharide and conjugate vaccines in older children and adults:

The effectiveness of meningococcal serogroup C polysaccharide vaccine was evaluated in two field trials which, in total, involved approximately 28,000 military recruits, and was shown to be 89% efficacious. Meningococcal serogroup A polysaccharide vaccines were evaluated in Egyptian children 6-15 years old in controlled fields trials. Effectiveness was approximately 90% during the first year after vaccination. Compared with older individuals, bactericidal antibody responses to meningococcal polysaccharide vaccines in children younger than 2 years were lower.

MenACWY-D immunologic non-inferiority was demonstrated in pre/adolescents (11-18 years old) (pre/adolescent) and in adults (18-55 years old), compared to MPSV4. Pre/adolescents and adults were enrolled in separate studies. In both studies, the co-primary endpoints were based on a serogroup-specific vaccine response (seroresponse), defined as a post-vaccination titer at least four-fold higher compared to baseline (pre-vaccination). A baby rabbit (BR) complement source was used in the assay. In pre/adolescents, SBA-BR seroresponses in both vaccine groups ranged from 92-93% for serogroup A, 89-92% for serogroup C, 95-97% for serogroup W135, and 80-82% for serogroup Y. In adults, SBA-BR seroresponses in both vaccine groups ranged from 81-85% for serogroup A, 89-90% for serogroup C, 90-94% for serogroup W135, and 74-79% for serogroup Y. Also, sera from a participant subset was tested to determine the similarity of MenACWY-D and MSPV4 bactericidal antibody responses, when a BR and when a human (H) complement source was used in the assay. In the adult trial, seroresponses among MenACWY and MPSV4 study groups showed general agreement, when either HC or BR was used. In pre/adolescents, SBA-H seroresponses for A,Y, and W135 was 90% or greater in both study groups, except for serogroup C in MPSV4 participants, which was 86%.[9]

Vaccine effectiveness among adolescents and young adults was estimated using a mathematical model approximately 3-4 years after MenACWY-D introduction in the U.S. In 2005, MenACWY-D was recommended by the U.S. Advisory Committee on Immunization Practices for routine pre/adolescents use. Immunizations were commonly given at the scheduled pre-adolescent visit 11-12 years old), at high school entry (15 years old) or to incoming college freshmen (17-18 years old). MenACWY-D was the preferred vaccine for routine immunization; at the time of the study, MPSV4 was the only available alternative. For both vaccines, a single dose was given. During 2005-2008, meningococcal disease due to serogroups C or Y were identified through active and enhanced passive population surveillance in the U.S. MenACWY-D effectiveness for disease due to serogroups C and Y was estimated to be 80% to 85%, which was consistent with the adolescent SBA-H seroresponse rates reported approximately 3 years after vaccination.[10]

MenACWY-CRM was licensed in the U.S. in 2010. MenACWY-CRM immunogenicity was demonstrated in pre/adolescents (11-18 years old) and adults (19-55 years old) compared to MenACWY-D. The co-primary endpoints for each age group were based on a serogroup-specific composite seroresponse: a post-vaccination SBA-H titer $\geq$1:8, for participants with a pre-vaccination SBA-H titer < 1:4, or, a post-vaccination titer as least four-fold higher than baseline, for participants with a pre-vaccination SBA-H titer $\geq$1:4. The pre-specified criteria for each of co-primary endpoints were met. Post-licensure effectiveness of this vaccine in adolescents and adults cannot be estimated yet due to the limited time the product has been available.

3. Experience with use of polysaccharide-protein conjugate vaccines in infants and toddlers

Hemophilus influenzae type b (Hib) conjugate vaccines have been successfully used to prevent invasive disease due to Hib, especially in young children. Conjugate vaccine-induced antibody responses were protective, compared to immune responses elicited by corresponding polysaccharide vaccines, in children < 2 years old because capsular polysaccharide antigens, when conjugated to a carrier protein, were more immunogenic. Pneumococcal and meningococcal C conjugate vaccines, developed using the similar conjugation techniques, were also effective in controlling pathogen-specific disease.[11;12]

Meningococcal group C conjugate vaccines were shown in pre-authorisation clinical trials to elicit bactericidal antibodies in all age groups. Introduction of conjugate meningococcal C (MenC) vaccines and use in mass immunization programs occurred in Canada and several European countries. Vaccination coverage was maintained via routine infant MenC immunizations. Population-based surveillance data supported an association between widespread MenC conjugate vaccine use and declines in disease incidence.[12-14] Sero-epidemiological data from United Kingdom population-based studies showed that, in previously vaccinated infants, decreases in circulating anti-meningococcal C antibodies corresponded with reduced vaccine effectiveness and MenC disease recurrence. An additional dose of meningococcal C conjugate vaccine, given in the second year of life, afterwards resulted in longer bactericidal antibody persistence.[12]

4. Serum bactericidal antibody (SBA) assay

Functional antibody
The bactericidal activity of serum from vaccine recipients is a suitable surrogate for evaluating vaccine effectiveness of meningococcal vaccines because complement mediated bacterial killing by bactericidal antibodies is a primary mechanism of protection against meningococcal disease. The role of antibodies in natural immunity to meningococcal disease was established by Goldschneider et al. The presence of anti-meningococcal antibodies, measured by serum bactericidal activity (SBA-H titer $\geq$1:4) using an intrinsic human complement source in the assay, was indicative of protection against systemic meningococcal infection.[4]

Assay method
The principle of the serum bactericidal assay is based on antibody-mediated complement-dependent lysis of *N meningitidis* strains by antibodies in serum samples. Anti-meningococcal antibodies present in the serum activate a complement pathway that results in cell lysis (bactericidal activity), which is the same mechanism by which antibodies *in vivo* confer immunity against meningococcal disease. The serum bactericidal titer is reported as the reciprocal serum dilution at which $\geq$50% of cells are lysed, compared to the number of cells present prior to incubation with clinical sera and complement.

Complement source

Bacterial antibodies present in serum, using a human or a baby rabbit complement source in the assay, indicates functional activity. Importantly, the source of complement affects the reported outcome measure. Compared to human sera, use of rabbit sera as a source of complement generally results in higher reported SBA titers. Notably, for some serogroups and/or age groups, there is often no predictable correlation or agreement between bactericidal titers generated with an assay using a rabbit complement source vs. a human complement source, most likely because certain components of the complement cascade are species specific.

Summary

VRBPAC was last consulted regarding approaches to licensure of meningococcal conjugate vaccines in 1997. At that time the committee concurred with use of bactericidal activity as the basis of inferring effectiveness for serogroups A, C, Y, and W-135 when used to compare new conjugate vaccines to the licensed polysaccharide vaccine in individuals older than 2 years of age. No meningococcal vaccine is currently licensed for use in children under 2 years of age, so studies comparing to a licensed vaccine are not possible in this age group. Evidence supporting use of pre-specified anti-meningococcal bactericidal antibody titers measured using a human complement source for inferring effectiveness in infants and young children is presented in this document and will be reviewed when VRBPAC convenes on April 6, 2011. CBER is seeking concurrence from VRBPAC for this approach, and advice regarding any additional information that may be needed.

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